

REMARKS**I. Status of the claims**

Claims 1--34, 36-69, 71-142, and 144-151, and 153-168 are pending in the application, and stand rejected. Claims 1, 26, 69, 82, 130 and 143 are amended herewith. Claims 70 and 143 have previously been canceled, and claims 35 and 152 have been canceled herewith without prejudice.

II. Amendments to the claims

Claim 1 has been amended to state that the fusogenic liposome is an N-acyl phosphatidylethanolamine. Support for this amendment can be found, for example, in claim 35 as filed.

Applicants have amended claim 26 to recite "interfering RNA" instead of "RNA interference." Applicants submit that one of ordinary skill in the art would have understood that "RNA interference" refers to a nucleic acid, not "a phenomenon." Furthermore, of the specification, which states that the nucleic acid can be "RNA interference, i.e., RNA_i," *Specification* at ¶96. "RNA_i" is routinely used in the art to refer to interfering RNA.

Applicants have amended claim 82 to recite "C₁-C₃ alcohol." Support for this amendment can be found, for example, at paragraph 90 of the specification.

Claims 69 and 142 have been amended to more specifically claim the invention. No new matter has been added by these amendments.

III. Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1-12, 14-69, 71-86, 88-142 and 144-168 under §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *Office Action* at p. 3. According to the

Examiner, these claims are indefinite because “the metes and bounds of ‘aqueous medium Z1’ are unclear.” *Office Action* at p. 3. Applicants respectfully traverse. The phrase “aqueous medium Z1” merely identifies the aqueous medium relative to, for example, aqueous medium Z2 in claim 1 as originally filed. Similarly, the phrase “aqueous medium Z1” identifies the aqueous medium relative to aqueous medium Y recited in claim 141. Withdrawal of this rejection is respectfully requested.

The Examiner states that claim 26 is indefinite for reciting “wherein the RNA is . . . RNA interference.” *Office Action* at p. 3. This rejection has been obviated by the amendment of claim 26 to recite “interfering RNA,” as explained in section II of this paper.

The Examiner states that claim 82 is indefinite for reciting “C₁-C₃ alcohol.” This rejection has been obviated by the amendment of claim 82 to recite “C₁-C₃ alcohol,” as explained in section II of this paper.

The Examiner states that claim 145 is indefinite because it “requires an aqueous buffer but simultaneously disallows any hydrating agent.” According to the Examiner, “an aqueous buffer is a hydrating agent, so the claim is indefinite.” *Office Action* at p. 3. Applicants respectfully traverse. The specification states:

The hydrating agent is a compound having at least two ionizable groups, one of which ionizable groups is capable of forming an easily dissociative ionic salt, which salt can complex with the ionic functionality of the liposome-forming lipid. The hydrating agent inherently does not form liposomes in and of itself and the hydrating agent must also be physiologically acceptable. Preferably, the at least two ionizable groups of the hydrating agent are of opposite charge. Examples of the hydrating agent are arginine, homoarginine, .gamma.-aminobutyric acid, glutamic acid, aspartic acid and similar amino acids.
Specification at ¶ 74.

Thus, the “hydrating agent” recited in claim 145 is clearly described in the specification, and furthermore, does not encompass an aqueous buffer. Therefore, the claim is not indefinite.

The Examiner states that claim 130 is indefinite for reciting “up to about 1 of the weight of the gel.” Applicants have amended claim 130 to recite “1%.” Support for this amendment can be found, for example, in claim 57, which recites “up to about 1% of the weight of the gel.”

Based on the amendments and arguments set forth above, Applicants respectfully request withdrawal of the §112, second paragraph, rejection.

The Examiner has rejected claim 152 under § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Solely to expedite prosecution, Applicants have canceled claim 152. Accordingly, this rejection has been obviated.

IV. Rejections under 35 U.S.C. § 102(b)

A. Eppstein

The Examiner has rejected claims 1-34, 38-69, 71-73 and 147-168 as being anticipated by U.S. Patent No. 4,897,355 to Eppstein et al. (“Eppstein”) as evidenced by GenBank Accession No. M77788. *Office Action* at p. 7. To anticipate a claim under §102(b), a reference must teach each and every element of the claim, either expressly or inherently. M.P.E.P. § 2131. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union oil Co. of California*, 8144. F. 2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, “[t]he identical invention must be shown in as complete detail as contained in the . . . claim.” *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

Eppstein describes lipophilic cationic compounds of Formula I. *Eppstein* at abstract and col. 3, ll. 14-34. Eppstein further describes a liposome formulation comprising up to 10% by weight of a biologically active substance, 1% to 20% by weight of a lipid component comprising a compound

of Formula I in a quantity of from about 1% to 100% by weight, and an aqueous solution in a quantity sufficient to make 100% by volume. *Id.* at col. 3, ll. 35-46. Importantly, Eppstein does not disclose an N-acyl phosphatidyl ethanolamine, as now recited in amended claim 1. Therefore, Eppstein does not disclose each and every element of the instant claims.

Because claims 2-34, 38-69, 71-73 and 147-168 all depend from claim 1, there claims also are not anticipated by Eppstein. Withdrawal of this rejection is respectfully requested.

B. Papahadjopolous

The Examiner has rejected claims 1-16, 25, 29-31, 33, 34, 38-69, 71-80, 87, 88, 90, 99, 102-104, 106, 107, 123, 141, 142, 144, 147 and 153-168 as being anticipated by U.S. Patent No. 4,235,871 to Papahadjopolous ("Papahadjopolous"), as evidenced by U.S. Publication No. 20050025821 to Harvie et al. ("Harvie"). *Office Action* at p. 8. The Examiner states that Papahadjopolous teaches "a variety of liposomes comprising nucleic acids . . .," and that "[t]he liposomes may consist of a fusogenic lipid such as dioleoylphosphatidylethanolamine (DOPE) or phosphatidyl serine (PS)" *Id.* The Examiner states that "Harvie provides evidence that PS is a fusogenic liposome. *Id.* Applicants respectfully traverse.

Papahadjopolous describes a method of encapsulating biologically active materials in lipid vesicles. In particular, the method of Papahadjopolous comprises in part "providing a mixture of a vesicle wall forming compound in organic solvent and an aqueous mixture of the biologically active material to be encapsulated, the ratio of organic phase to aqueous phase being that which will produce an emulsion of the water in oil type" *Papahadjopolous* at col. 3, ll. 1-5. Papahadjopolous fails to disclose N-acyl phosphatidyl ethanolamine, as recited in independent

claim 1. Therefore, Papahadjopolous does not anticipate claims 1-16, 25, 29-31, 33, 34, 38-69, 71-73, 147 and 153-168.

Papahadjopolous teaches that the organic solvent used in making liposomes is one “in which an aqueous phase does not have an appreciable solubility.” *Id.* at col. 4, ll. 48-52. According to Papahadjopolous, the aqueous phase is added to the organic phase “to obtain a 2-phase mixture.” *Id.* at col. 5, ll. 14-20 (emphasis added). “The heterogeneous 2-phase mixture obtained . . . is emulsified to obtain an emulsion of the character produced by ultrasonic radiation.” *Id.* at col. 5, ll. 42-44 (emphasis added). The present specification, in contrast, states that the water miscible organic solvent “when mixed with water forms a homogenous liquid, i.e., with one phase.” *Specification* at ¶ 90. Thus, Papahadjopolous fails to disclose a water-miscible organic solvent, as recited in independent claim 74. Rather, the organic solvents described by Papahadjopolous form *heterogeneous* mixtures with aqueous media. For at least these reasons, Papahadjopolous fails to describe each and every limitation of claims 74-80, 87, 88, 90, 99, 102-104, 106, 107, 123, 141, 142, and 144. Withdrawal of this rejection is respectfully requested.

V. Rejections under 35 U.S.C. § 103

A. Papahadjopolous

The Examiner has rejected claims 74, 89, 111-140 and 146 as being obvious over Papahadjopolous. The Examiner states that Papahadjopolous teaches “a method of making liposomes by combining lipids . . . and nucleic acids in an inert to form an emulsion, thereafter forming a gel, and finally converting the gel to a suspension of liposomes by addition of an aqueous medium.” *Office Action* at p. 10.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that “obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. “The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528.

As discussed in section IV of this paper, Papahadjopolous fails to disclose a water-miscible solvent. Rather, Papahadjopolous teaches that the organic solvent must form a heterogeneous mixture with aqueous media. *Papahadjopolous* at col. 5, ll. 14-16. Papahadjopolous also teaches that representative solvents are those “in which an aqueous phase does not have appreciable solubility.” *Id.* at col. 4, 48-52.

Applicants respectfully remind the Examiner that in an obviousness inquiry, a reference must be considered as a whole, including disclosures that away from the claimed invention. M.P.E.P. § 2142.02. Under *KSR*, “teaching away” still provides evidence of non-obviousness. See 127 S.Ct. at 1745. “[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness.” M.P.E.P. §2145 (citing *in re Hedges*, 783 F.2d 1083 (Fed. Cir. 1986)). If when combined, the references “would produce a seemingly inoperative device,” then they teach away

from their combination. *Tec Air, Inc. v. Denso Mfg. Michigan, Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). *See also, In re Fritch*, 972 F. 2d 1260, 1265 n. 12 (Fed. Cir. 1982) (“A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.”).

Papahadjopolous stresses the importance of the emulsification step, which requires a non-water-miscible organic solvent:

The emulsification of the initial aqueous phase into the organic phase, and the removal of the organic phase prior to the addition of any excess aqueous phase is essential for high capture percentage in this method and is a critical difference between the process of our invention and all previous methods heretofore described. *Papahadjopolous* at col. 6, ll. 56-63.

Based on these teachings, one skilled in art would have understood that a water immiscible solvent must be used in Papahadjopolous’ method. Furthermore, these teachings suggest that a water-miscible solvent would render the Papahadjopolous process inoperable for its intended purpose since the solvent is, at least in part, “essential” for high capture percentage. For at least reasons, Applicants respectfully request withdrawal of this rejection.

B. Papahadjopolous in view of Eppstein

The Examiner has rejected claims 1, 17-24, 26-28, 33, 91-98, 100, 101 and 105 as being obvious over Papahadjopolous in view of Eppstein. The Examiner notes that Papahadjopolous does not teach plasmid DNA or oligonucleotides. According to the Examiner, “[i]t would have been obvious . . . to use the method of Papahadjopolous to encapsulate the plasmid or oligonucleotides of Eppstein because Papahadjopolous suggests that the liposome will protect nucleic acids from degradation . . . and because one of ordinary skill would clearly appreciate their utility for this purpose in view of the teachings of Eppstein. *Office Action* at p. 12.

Applicants note that Eppstein and Papahadjopolous, either alone or in combination do not disclose N-acyl phosphatidyl ethanolamines, as recited in claim 1.

Regarding the presently claimed methods, Applicants note that the Examiner has rejected dependent claims 91-98, 100, 101 and 105, but has not explained why Papahadjopolous in view of Eppstein renders independent claim 74 obvious. If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Furthermore, the teachings of Eppstein fail to remedy the deficiencies in the method of Papahadjopolous, set forth above. Specifically, the combination of Eppstein and Papahadjopolous fails to teach or suggest mixing a gel or liquid comprising at least one liposome forming lipid, at least one fusogenic lipid, a water miscible organic solvent and at least one nucleic acid with an aqueous medium, as recited in claim 74. As explained above, Papahadjopolous teaches against the presently claimed method, which involves a water-miscible organic solvent, and Eppstein provides no teachings with respect to organic solvents that would remedy the deficiencies of Papahadjopolous. Accordingly, withdrawal of this rejection is requested.

C. Papahadjopolous in view of Meers

The Examiner has rejected claims 1, 35-37, 74 and 108-110 as being unpatentable over Papahadjopolous in view of U.S. Patent No. 4,235,871 to Meers et al. ("Meers"). The Examiner contends that "it would have been obvious to use the lipids of Meers in the liposomes of Papahadjopolous because Meers taught that it promotes membrane fusion." *Office Action* at p. 13. Applicants respectfully traverse.

As explained above, Papahadjopolous teaches against using a water-miscible organic solvent, as presently claimed. Meers fails to provide any teachings to remedy this deficiency. For at least these reasons, Applicants submit that Papahadjopolous in view of Meers fails to render the presently claimed methods obvious. Withdrawal of this rejection is respectfully requested.

D. Papahadjopolous in view of Lenk

The Examiner has rejected claims 81-86 as being unpatentable over Papahadjopolous in view of U.S. Patent No. 5,169,637 to Lenk et al. The Examiner notes that Papahadjopolous does not disclose acetone, ethanol, methanol or 2-propanol. The Examiner relies on Lenk for disclosing these solvents. *Office Action* at p. 14. According to the Examiner, it would have obvious to one of ordinary skill in the art to use “any solvent that could be substantially removed from the lipids.” *Id.* Citing the MPEP, the Examiner further states that “when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents.” *Id.* Applicants respectfully traverse.

As explained above, Papahadjopolous teaches against using water-miscible solvents. Specifically, Papahadjopolous explicitly directs the skilled artisan to use an organic solvent “in which an aqueous phase does not have appreciable solubility.” Applicants submit that a water-miscible organic solvent does not have the same function, and is not an art-recognized equivalent, of a solvent “in which an aqueous phase does not have appreciable solubility.” This is particularly true in view of Papahadjopolous’ emphasis on the criticality of using a solvent in which an aqueous phase does not have appreciable solubility. For at least these reasons, Applicants request withdrawal of this rejection.

VI. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-027.01.**

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Respectfully submitted,

/Hilary Dorr Lang/

Hilary Dorr Lang

Registration No.: 51,917

FOLEY HOAG LLP

155 Seaport Blvd

Boston, Massachusetts 02210

(617) 832-1223

Attorney for Applicants